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Lymphocytic Pleural Effusion Due to Crizotinib Usage

Krizotinib Kullanımına Sekonder Lenfositik Plevral Efüzyon

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Abstract

A 41-year-old woman with Anaplastic Lymphoma Kinase (ALK) gene positive adenocarcinoma of the lung presented with dyspnea in the 4th month of Crizotinib therapy with a prominent finding of bilateral mild pleural effusion. A comprehensive radiological and laboratory investigation discounted infection, rheumatological diseases and malignancies, while the symptoms and pleural effusion regressed after pausing Crizotinib medication. We present this unusual case of lymphocytic pleural effusion associated with Crizotinib, which is a novel tyrosine kinase inhibitor.

Keywords: *Crizotinib, lung cancer, pleural effusion.*

Öz

Anaplastik Lenfoma Kinaz (ALK) geni pozitif akciğer adenokarsinomu olan 41 yaşındaki bir kadın hasta, crizotinib tedavisinin dördüncü ayında nefes darlığı yakınması ile başvurdu. Radyolojik olarak bilateral hafif plevral efüzyonu olan hastada, kapsamlı radyolojik ve laboratuvar incelemelerinin ardından enfeksiyon, romatolojik hastalıklar, maligniteler gibi diğer yaygın nedenler dışlandı. Krizotinib ilacı kesildikten sonra semptomları ve plevral efüzyonunun gerilediği hatta steroid ile bu sürecin hızlandığı izlendi. Bu nedenle, bir tirozin kinaz inhibitörü olan krizotinib ile ilişkili alışılmadık bir lenfositik plevral efüzyon olgusunu sunmayı amaçladık.

Anahtar Kelimeler: *Krizotinib, akciğer kanseri, plevral efüzyon.*

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The echinoderm microtubule associated protein-like 4 (EML-4)-Anaplastic Lymphoma Kinase (ALK) oncogenic driver mutation appears in 2–7% of all cases of non–small-cell lung cancer (NSCLC) (1).

Crizotinib is an ALK inhibitor that was approved for the treatment of advanced-stage (IIIB and IV) lung adenocarcinoma patients with ALK (+) by the US Food and Drug Administration (FDA) in 2011, based on early phase clinical studies (2). Crizotinib is generally well tolerated even in older adult patients, with the most common side effects being gastrointestinal disorders and visual side effects, while peripheral edema, dizziness, tiredness, loss of appetite and interstitial pneumonia are less common (3,4).

Even it is seen rarely some drugs are one of the reasons of pleural effusion, and so for accurate diagnosis, the patients' drug history should be questioned in detail. Spontaneous recovery is generally observed after stopping treatment (4).

Diagnosis is based initially on a routine biochemical analysis of the pleural effusion to differentiate transudate/exudates, followed by a cytopathological and microbiological evaluation. Drug-induced pleural effusions are generally exudative with eosinophilic predominance in cell distribution.

Reports of pleural effusions associated with Crizotinib usage are rare in the literature. In one reported case, a 35-year-old woman with stage 4 ROS1-rearranged lung adenocarcinoma developed pleural effusion after four days of Crizotinib treatment. Examinations, including surgical thoracoscopy, pointed to no specific diagnosis, however, the effusion regressed after discontinuing Crizotinib (5). We present here the case of an ALK-positive lung adenocarcinoma patient with bilateral pleural effusion associated with Crizotinib treatment.

CASE

A 41-year-old female admitted with chest pain on right side was identified with a right hilar lesion and pleural effusion on right hemithorax (Figure 1A). Chest computed tomography revealed a 5 cm mass in right middle lobe, and pathology from a subsequent transthoracic needle aspiration biopsy confirmed lung adenocarcinoma. A FISH (Fluorescence in-situ hybridization) analysis of the tumor tissue was positive for an ALK rearrangement, and so Crizotinib therapy was initiated. Bilateral pleural effusion developed in the 3rd month that was more prominent on the right side (Figure 1B and 1C) that, when drained, revealed a regression of the primary lesion (Figure 1D). Ultrasound-guided thoracentesis was first performed on the left hemithorax, revealing the fluid to be serous and exudative, with no malignant cells observed on cytological examination. The effusion in the right hemithorax was drained using a pleural catheter, and the procedure was completed with talc pleurodesis. However, effusion in the right lung persisted, any malign cells were observed on cytoblock investigation for three times. The effusion on both sides contained a predominance of lymphocytic cells (Figure 2) that were negative for tuberculosis bacillus or any other microbiological agent. The patient's left ventricular function was normal on echocardiography, and antinuclear antibody testing was negative in fluid. Transdiaphragmatic fluid passage was excluded based on abdominal ultrasonography. Finally, the patient's drug usage was questioned, and she has stopped using diltiazem at first but effusion was persisted. Crizotinib treatment was suspended secondly, and a decrease in the amount of fluid was noted 15 days later. Methylprednisolone 40 mg/day was added to the treatment protocol to increase the patient's recovery rate. Her general medical condition improved, and she was started on Crizotinib again with frequent clinical and radiological follow-ups under steroid treatment. The amount of fluid did not increase as the steroid dose was tapered. While patient takes methylprednisolone 16 mg/day Crizotinib, left pleural fluid disappeared and right pleural thickening appeared due to talc pleurodesis (Figure 1E and 1F).

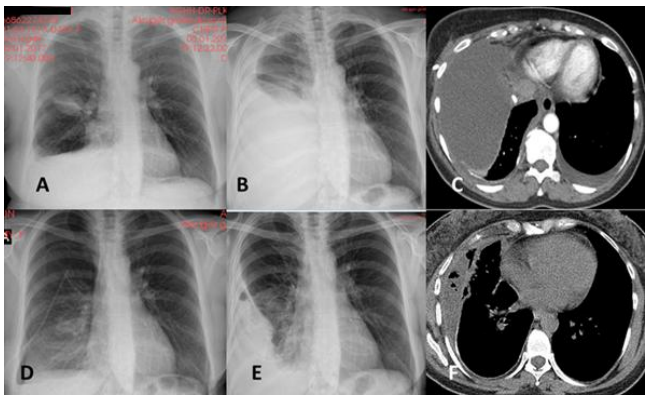

Figure 1: Chest X-ray on admission (A), Bilateral pleural effusion on Chest X-ray (B), Bilateral pleural effusion on CTT (C), Regression of primary lesion after effusion drainage (D), Complete response of pleural effusion on the left side and organized effusion on the right side (E), Regression of pleural effusion on CTT (F)

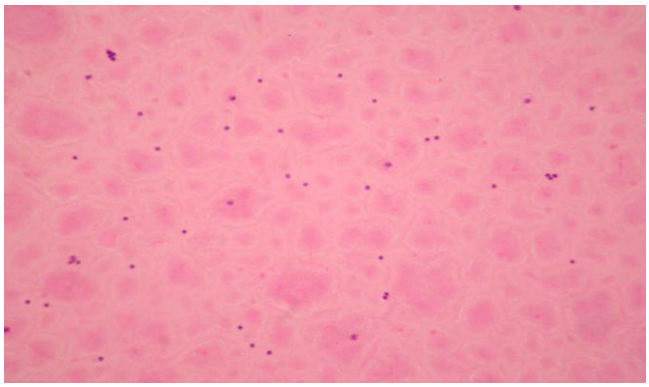

Figure 2: Cytological analyses of pleural liquid demonstrating lymphocyte infiltration (H&E X400)

DISCUSSION

Patients with lung cancer may develop increased pleural fluid as a side effect of chemotherapeutic agents (6). Drug related pulmonary toxicity is a common condition, in contrast to pleural effusion, which is more rare (7). As a result, drug-related sources of pleural effusion are largely overlooked.

Previous studies have reported varying times between the first dose of the suspected drug to the occurrence of pleural effusions, ranging from days to a decade (8). Drug dependent pleural effusions may be unilateral or bilateral, and may be accompanied by parenchymal lesions, fluid and/or systemic eosinophilia. If drug-dependent pleural effusion can be ruled out, the patient may be treated under a diagnosis of idiopathic pleural effusion (9).

On the 120th day of Crizotinib treatment, the patient's complained of shortness of breath. After eliminating such etiologies as infection, tuberculosis, malignant pleural effusion and collagen vascular disease, the lymphocytic predominance in the fluid led us to question the medication protocol.

Pleural effusion has been reported to occur due to the tyrosine kinase inhibitor (TKI) Desatinib. The underlying cause of pleural effusion related to Desatinib is immune response, for which the short term discontinuation of the drug, diuretic and steroid treatments is suggested (10). Other causes of lymphoplasmacytic pleural effusion include tuberculosis, viral pleurisy, rheumatoid diseases, cancer, chylothorax and asbestos exposure (9).

We attributed the increased pleural effusion in our patient to inflammatory response, supported by such findings as inflammatory cells in the pleural liquid, an absence of malignant cells in the pleural effusion, and the absence of clinical evidence of infection. In contrast to drug dependent interstitial lung diseases, drug-related pleural effusions are usually not life-threatening. In our case, the reinitiation of Crizotinib along with steroid treatment suppressed the patient's inflammatory process, preventing recurrence, and even initiating a rapid decrease. Literature contains several studies assessing Desatinib, from tyrosine kinase family, but none investigating Crizotinib (11).

The importance of the presented case lies in its identification of the relationship between the ALK inhibitor and pleural effusion. Pleural effusions associated with TKIs should be evaluated carefully, with considering possible drug reaction and "disease progression decision" should be made after careful cytological evolution.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - P.A.K., D.K., S.K., T.İ.C., Ş.Y., Ü.Y.; Planning and Design - P.A.K., D.K., S.K., T.İ.C., Ş.Y., Ü.Y.; Supervision - P.A.K., D.K., S.K., T.İ.C., Ş.Y., Ü.Y.; Funding -.; Materials -; Data Collection and/or Processing - T.İ.C., S.K., D.K.; Analysis and/or Interpretation - P.A.K., Ü.Y.; Literature Review - Ş.Y.; Writing - P.A.K.; Critical Review - Ü.Y.

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